

REMARKS

The specification has been amended to correct obvious typographical errors, and to correct the numbering of the figures. No new matter is added herein.

Claims 1-13, 27, 28 and 31-36 are currently pending in the application. Applicants acknowledge and thank the Examiner for withdrawing certain rejections from the Office Action of December 5, 2007. Claim 1 is amended to specify that the recited placental stem cells form tube-like structures, and branching thereof. Support for this amendment is found in the specification at least in Example 2. Claim 13 is amended to specify an *in vitro* method, and to specify particular control conditions. Support for this amendment is found in the Examples. Upon entry of the present Amendment, claims 1-13, 27, 28 and 31-36 will be pending.

Applicants respectfully request entry of this Amendment under 37 C.F.R. § 1.116(b)(2), as the claims have been amended to place them in better condition for appeal. Additionally, the amendments made herein are clarifying and should not require new search or consideration.

The Rejections Under 35 U.S.C. § 102(e) Should Be Withdrawn

Claim 13 is rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Drake *et al.*, WO 01/63281 (“Drake”). Office Action at pages 7-9. To establish anticipation under 35 U.S.C. § 102(b), the rejection must establish that each and every limitation of the claim is disclosed in the cited reference, either expressly or inherently. *See Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987).

Without conceding the propriety of the rejection, Applicants have amended claim 13 to specify that the claimed method is an *in vitro* method. Drake does not anticipate claim 13 as amended. Example 10, cited by the rejection, discloses a hypothetical *in vivo* method. Example 10, therefore, does not disclose the claimed method. The rejection also contends that Drake discloses that “potency of an agent can be determined by measuring tumor growth; an amount that slows or prevents tumor growth would be a therapeutically effective amount of an agent that inhibits neovascularization (p. 15, lines 17-20).” However, claim 13 requires an assessment of the extent of microvessel outgrowth from a vessel ring, not tumor growth. Drake fails to teach a determination of microvessel outgrowth from a vessel ring. For the above reasons, Drake does not teach all of the limitations of claim 13, and therefore, does not anticipate claim 13.

Applicants respectfully request that this rejection of claim 13 be withdrawn.

The Rejections Under 35 U.S.C. § 103 Should Be Withdrawn

Claims 1, 27 and 28 are rejected under 35 U.S.C. § 103 as obvious over Drake in view of Zygmunt, *Early Pregnancy* 5(1):72-73 (2001). Office Action at pages 9-11.

A determination of obviousness requires analysis of “1) ‘the scope and content of the prior art’; 2) the ‘differences between the prior art and the claims’; 3) ‘the level of ordinary skill in the pertinent art’; and 4) ‘objective evidence of nonobviousness’.” *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1734 (2007) (quoting *Graham v. John Deere & Co. of Kansas City*, 86 S. Ct. 684 (1966)). In rejecting a claim for obviousness, the rejection “must explain why the difference(s) between the prior art and the claimed invention would have been obvious to one of ordinary skill in the art.” “Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*,” 72 Fed. Reg. 57526, 57528 (2007) (“Guidelines”); see also MPEP, Section 2100 at page 2100-118. Applicants note that the “teaching, suggestion or motivation” element was not obviated by *KSR*; see, e.g., *Takeda Chemical Indus., Ltd. v. AlphaPharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007). Additionally, “[r]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” Guidelines at pages 57258-59, citing *KSR*; see also MPEP at page 2100-119, left column. In reviewing the claims for obviousness, the rejection must avoid impermissible hindsight, and determine the obviousness of the invention to a person of skill in the art at the time the invention was made, based only on the prior art and not on Applicant’s disclosure. See MPEP at page 2100-121 and 2100-127.

Respectfully, the rejection has not made out the required *prima facie* case of obviousness. In particular, the rejection still has not established that the endothelial progenitor cells mentioned in—but not described—by Zygmunt are the recited placental stem cells, which are CD34⁻, for the reasons already of record. The present rejection does not contest that Urbich, *Circulation Res.* 95:343-353 (2004) teaches that angioblasts (endothelial progenitor cells) are CD34⁺. As such, Urbich demonstrates that Zygmunt teaches away from the claimed invention.

The rejection, instead, cites Urbich as teaching that “[t]here is increasing evidence that *myeloid cells* can co-express endothelial markers and form tube-like structures ex vivo” (p. 344, col. 1, para. 3; emphasis added), then *assumes* that myeloid cells that are CD34⁻ must also be each of CD10⁺, CD29⁺, CD38⁻, CD44⁺, CD45⁻, CD54⁺, CD90⁺, SH2⁺, SH3⁺, SH4⁺, OCT-4⁺, SSEA-3⁻ and SSEA-4⁻. Office Action, pages 10-11. Respectfully, however, this

line of reasoning does not establish—or even attempt to demonstrate—that the *myeloid cells* of Urbich are the *endothelial progenitor cells* mentioned in Zygmunt. Indeed, the rejection appears to abandon the contention that the endothelial progenitor cells, the only cells arguably disclosed in Zygmunt, are responsible for vascularization, focusing now on a different type of cell, myeloid cells.

This line of reasoning further does not establish that the myeloid cells of Urbich, or the endothelial progenitor cells of Zygmunt are the placental stem cells recited in claims 1, 27 and 28. The rejection provides no reason why a person of ordinary skill in the art would believe the recited placental stem cells to be myeloid cells. Moreover, the rejection still has provided no basis for asserting that the cells mentioned in Zygmunt are *each* of OCT-4⁺, SSEA-3⁻ and SSEA-4⁻, as recited in claim 27, or *each* of CD10⁺, CD29⁺, CD34⁻, CD38⁻, CD44⁺, CD45⁻, CD54⁺, CD90⁺, SH2⁺, SH3⁺, SH4⁺, OCT-4⁺, SSEA-3⁻ and SSEA-4⁻, as recited in claim 28. Again, the rejection must provide a rationale or evidence tending to show inherency. MPEP, Section 2100 at page 2100-47. The rejection must also show that the missing feature(s) would *necessarily* be present in the thing described in the cited art, and that it would be so recognized by persons of ordinary skill in the art. *Id*, right column. The rejection simply has not established either that the markers recited in the claims are necessarily present on the cells allegedly disclosed in Zygmunt or in Drake, or in Urbich, or that a person of skill in the art would recognize them to be present.

Therefore, for the reasons above, and the reasons cited in the response to the prior non-final Office Action, the cited combination of references fails to teach a method of identification of a modulator of angiogenesis comprising contacting placental stem cells with a test compound, as recited in the amended claims, and, as a result, fails to render invention of the amended claims obvious. Withdrawal of this rejection is respectfully requested.

The Rejection Under 35 U.S.C. § 112, Second Paragraph Should Be Withdrawn

Claims 13 and 32 are rejected under 35 U.S.C. § 112, second paragraph as indefinite because the “relationship between the plurality of tumor cells and the microvessel outgrowth from the vessel section” is allegedly unclear. Office Action at pages 11-12. A claim is definite if one of ordinary skill in the art can discern the claims meaning so as to avoid infringement. *See, e.g., Metabolite Labs., Inc. v. Lab Corp. of Am. Holdings*, 370 F.3d 1354, 1366 (Fed. Cir. 2004) (“The requirement to ‘distinctly’ claim means that the claim must have a meaning discernible to one of ordinary skill in the art when construed according to correct principles . . . Only when a claim remains insolubly ambiguous without a discernible

meaning after all reasonable attempts at construction must a court declare it indefinite.”); see also *Bancorp Services L.L.C. v. Hartford Life Ins. Co.*, 359 F.3d 1367, 1372 (Fed. Cir. 2004).

Without conceding the propriety of the rejection, claim 13 is amended herein to specify that the vessel section is cultured *with* a plurality of tumor cells. As such, it is clear that the tumor cells would “contribute to the conditions which allow microvessel outgrowth from the vessel section . . . ” Office Action at page 12. Further, claim 13 is amended to specify that the control conditions require the presence of tumor cells. As such, the claim is definite because a person of skill in the art would not find the claims “insolubly ambiguous.” Withdrawal of this rejection of the claims is respectfully requested.

The Rejection Under 35 U.S.C. § 112, First Paragraph Should Be Withdrawn

Claims 1-12, 27, 28, 31 and 33-36 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly nonenabled. Office Action at pages 12-15. Specifically, the rejection contends that the specification does not “demonstrate[] that the CD34⁻ placental stem cells would actually produce or differentiate into microvessels. The closest demonstration of a structural change is the tube formation . . . and the branching form . . . ” Office Action at page 14. Applicants traverse as follows.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in the patent coupled with information known in the art without undue experimentation. *U.S. v. Teletronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988). The test is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. See *In re Angstadt*, 190 USPQ 214, 219 (C.C.P.A. 1976). The Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. MPEP § 2164.04, (citing *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993)). Furthermore, “[a] specification disclosure...must be taken as being in compliance with the enablement requirement...unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.” *Id.* (emphasis added). All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art.” MPEP § 2164.08 (emphasis added).

The claims as amended are enabled. Without conceding the propriety of the rejection, claim 1, from which the remaining rejected claims ultimately depend, has been amended to specify that the recited placental stem cells form tube-like structures. Example 2 demonstrates that embryonic-like stem cells, when cultured under the conditions disclosed in

the Example, express endothelial markers such as smooth muscle-specific myosin heavy chain and nestin, which are indicative of angiogenesis. *See* at least page 64 and Table 2 of the specification as filed. The cells also develop tube-like structures, which can exhibit branching or bifurcation. *See* at least Example 1, Section 6.2.2, Table 4, and FIG. 3. The “embryonic like stem cells” are CD34⁻ placental stem cells; see at least page 47 of the specification as filed. Thus, the specification clearly demonstrates that CD34⁻ placental stem cells can form tube-like structures, which can form bifurcations and branching. Examples 1 and 2 also teach the modulation of formation of such tube-like structures and branching. As such, a person of skill in the art would need to perform no undue experimentation in order to perform the claimed method, and the claims as amended are enabled.

Applicants respectfully request that this rejection of the claims be withdrawn.

CONCLUSION

Applicants respectfully request that the present remarks be made of record in the file history of the present application. An early allowance of the application is earnestly requested. The Examiner is invited to contact the undersigned with any questions concerning the application. Should any fee be required for this paper, other than the extension of time to be paid via EFS-Web, please charge the necessary amount to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

Date: October 2, 2008

By: Lawrence S. Graham
For: Anthony M. Insogna

Reg. No. 49,020
Reg. No. 35,203

JONES DAY
222 East 41st Street
New York, New York 10017
(212) 326-3939